Approval Date: MAY -8 2008

FREEDOM OF INFORMATION SUMMARY

EtoGesic® (etodolac) Tablets

Supplemental NADA 141-108

Fort Dodge Animal Health

Allows for the addition of a 500 mg tablet

NADA 141-108

FOIS

FREEDOM OF INFORMATION SUMMARY

1. *GENERAL INFORMATION:*

a. File Number:	NADA 141-108
b. Sponsor:	Fort Dodge Animal Health P.O. Box 1339 Fort Dodge, Iowa 50501 Drug Labeler Code: 053501
c. Established Name:	Etodolac
d. Proprietary Name:	EtoGesic® Tablets
e. Dosage Form:	Tablet
f. How Supplied:	Each tablet size is scored and is available in bottles of 7, 30, and 90 tablets.
g. How Dispensed:	Rx
h. Amount of Active Ingredients:	150 mg, 300 mg, and 500 mg etodolac.
i. Route of Administration:	Oral
j. Species/Class:	Canine
k. Recommended Dosage:	10 to 15 mg/kg body weight (4.5 to 6.8 mg/lb) given orally once daily.
l. Pharmacological Category:	Non-steroidal anti-inflammatory drug
m. Indications:	For the management of pain and inflammation associated with osteoarthritis in dogs.
n. Effect of Supplement:	This supplement allows for the addition of a 500 mg tablet.

2. *EFFECTIVENESS:*

The approval of the larger size tablet containing 500 mg etodolac does not require new effectiveness data, as the minimum dose remains the same as currently approved. The approval is based on the manufacturing information on containers/closures,

labeling, dissolution and stability of the new larger size tablets. Refer to the FOI Summary for the original approval dated July 22, 1998.

3. *TARGET ANIMAL SAFETY:*

The approval of the larger size tablet containing 500 mg etodolac does not require new target animal safety data, as the maximum dose remains the same as currently approved. The approval is based on the manufacturing information on containers/closures, labeling, dissolution and stability of the new larger size tablets. Refer to the FOI Summary for the original approval dated July 22, 1998.

4. *HUMAN SAFETY:*

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this supplemental NADA.

Human warnings are provided on the product label as follows: "Keep out of reach of children" and "Not for human use."

5. *AGENCY CONCLUSIONS:*

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrates that EtoGesic® Tablets, when administered orally, are safe and effective for the management of pain and inflammation associated with osteoarthritis in dogs.

This supplement is a Category II change under the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(ii). The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

6. *ATTACHMENTS:*

Facsimile Labeling is attached as indicated below:
a. Bottle labels for 7, 30, and 90 count bottles.
b. Package insert

Approval Date: MAY -8 2008

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a. Bottle labels for 7, 30, and 90 count bottles.
b. Package insert

5530F

EtoGesic®

READ BEFORE USING THIS PRODUCT

85%

NADA 141-108, Approved by FDA

FORT DODGE®

EtoGesic®

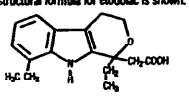
(etodolac)

TABLETS FOR ORAL USE IN DOGS ONLY

Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Etodolac is a pyranocarboxylic acid, chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid. The structural formula for etodolac is shown:



The empirical formula for etodolac is $C_{17}H_{21}NO_3$. The molecular weight of the base is 287.37. It has a pKa of 4.65 and an *n*-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol. Each tablet is biconvex and half-scored and contains either 150, 300 or 500 mg of etodolac.

PHARMACOLOGY

Etodolac is a non-narcotic, nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, anti-pyretic, and analgesic activity. The mechanism of action of etodolac, like that of other NSAIDs, is believed to be associated with the inhibition of cyclooxygenase activity. Two unique cyclooxygenases have been described in mammals[1]. The constitutive cyclooxygenase, COX-1, synthesizes prostaglandins necessary for normal gastrointestinal and renal function. The inducible cyclooxygenase, COX-2, generates prostaglandins involved in inflammation. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity, while inhibition of COX-2 provides anti-inflammatory activity. In *in vitro* experiments, etodolac demonstrated more selective inhibition of COX-2 than COX-1[2]. Etodolac also inhibits macrophage chemotaxis *in vivo* and *in vitro*[3]. Because of the importance of macrophages in the inflammatory response, the anti-inflammatory effect of etodolac could be partially mediated through inhibition of the chemotactic ability of macrophages.

Pharmacokinetics in healthy beagle dogs: Etodolac is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. The extent of etodolac absorption (AUC) is not affected by the prandial status of the animal. However, it appears that the peak concentration of the drug decreases in the presence of food. As compared to an oral solution, the relative bioavailability of the tablets when given with or without food is essentially 100%. Peak plasma concentrations are usually attained within 2 hours of administration. Though the terminal half-life increases in a nonfasted state, minimal drug accumulation (less than 30%) is expected after repeated dosing (i.e., steady-state). Pharmacokinetic parameters estimated in a crossover study (fed vs. fasted) in eighteen 5-month old beagle dogs are summarized in the following table:

Mean Pharmacokinetic Parameters Estimated in 18 Beagle Dogs After Oral Administration of 150 mg of Etodolac (approximately 12-17 mg/kg)

Pharmacokinetic Parameter	Tablet/ Fasted	Tablet/ Nonfasted
C_{max} (µg/mL)	22.0±6.42	16.9±8.84
T_{max} (hours)	1.69±0.69	1.08±0.46
$AUC_{0-\infty}$ (µg•hours/mL)	64.1±17.9	63.9±28.9
Terminal half-life, $t_{1/2}$ (hrs)	7.66±2.05	11.98±5.52

Pharmacokinetics in dogs with reduced kidney function: In a study involving four beagle dogs with induced acute renal failure, there was no observed change in drug bioavailability after administration of 200 mg single oral etodolac doses. In a study evaluating an additional four beagles, no changes in electrolyte, serum albumin/total protein and creatinine concentrations were observed after single 200 mg doses of etodolac. This was not unexpected since very little etodolac is cleared by the kidneys in normal animals. Most of etodolac and its metabolites are eliminated via the liver and feces. In addition, etodolac is believed to undergo enterohepatic recirculation[4].

EFFICACY

A placebo-controlled, double-blinded study demonstrated the anti-inflammatory and analgesic efficacy of EtoGesic (etodolac) tablets in various breeds of dogs. In this clinical field study, dogs diagnosed with osteoarthritis secondary to hip dysplasia showed objective improvement in mobility as measured by force plate parameters when given EtoGesic tablets at the label dosage for 8 days.

INDICATIONS

EtoGesic is recommended for the management of pain and inflammation associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION

The recommended dose of etodolac in dogs is 10 to 15 mg/kg body weight (4.5 to 6.8 mg/lb) administered once daily. Due to tablet sizes and scoring, dogs weighing less than 5 kg (11 lb) cannot be accurately dosed. The effective dose and duration should be based on clinical judgment of disease condition and patient tolerance of drug treatment. The initial dose level should be adjusted until a satisfactory clinical response is obtained, but should not exceed 15 mg/kg once daily. When a satisfactory clinical response is obtained, the daily dose level should be reduced to the minimum effective dose for longer term administration.

CONTRAINDICATIONS

EtoGesic is contraindicated in animals previously found to be hypersensitive to etodolac.

PRECAUTIONS

Treatment with EtoGesic tablets should be terminated if signs such as inappetence, emesis, fecal abnormalities, or anemia are observed. Dogs treated with nonsteroidal anti-inflammatory drugs, including etodolac, should be evaluated periodically to ensure that the drug is still necessary and well tolerated.

EtoGesic, as with other nonsteroidal anti-inflammatory drugs, may exacerbate clinical signs in dogs with pre-existing or occult gastrointestinal, hepatic or cardiovascular abnormalities, blood dyscrasias, or bleeding disorders.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of etodolac with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Studies to determine the activity of EtoGesic tablets when administered concomitantly with other protein-bound drugs have not been conducted in dogs. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.

The safety of EtoGesic has not been investigated in breeding, pregnant or lactating dogs or in dogs under 12 months of age.

INFORMATION FOR DOG OWNERS

EtoGesic, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include decreased appetite, vomiting, diarrhea, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes. **Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue EtoGesic therapy and contact their veterinarian immediately if signs of intolerance are observed.** The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow-up for all dogs during administration of any NSAID.

WARNINGS

Keep out of reach of children. Not for human use. Consult a physician in cases of accidental ingestion by humans. **For use in dogs only.** Do not use in cats.

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish hematological and serum biochemical baseline data prior to, and periodically during, administration of any NSAID should be considered. **Owners should be advised to observe for signs of potential drug toxicity (see Information for Dog Owners and Adverse Reactions).**

ADVERSE REACTIONS

In a placebo-controlled clinical field trial involving 116 dogs, where treatment was administered for 8 days, the following adverse reactions were noted:

Adverse Reaction	EtoGesic Tablets % of Dogs	Placebo % of Dogs
vomiting	4.3%	1.7%
regurgitation	0.9%	2.6%
lethargy	3.4%	2.6%
diarrhea/loose stool	2.6%	1.7%
hypoproteinemia	2.6%	0
urticaria	0.9%	0
behavioral change, urinating in house	0.9%	0
inappetence	0.9%	1.7%

Following completion of the clinical field trial, 92 dogs continued to receive etodolac. One dog developed diarrhea following 2-1/2 weeks of treatment. Etodolac was discontinued until resolution of clinical signs was observed. When treatment was resumed, the diarrhea returned within 24 hours. One dog experienced vomiting which was attributed to treatment, and etodolac was discontinued. Hypoproteinemia was identified in one dog following 11 months of etodolac therapy. Treatment was discontinued, and serum protein levels subsequently returned to normal.

Post-Approval Experience:

As with other drugs in the NSAID class, adverse responses to EtoGesic tablets may occur. The adverse drug reactions listed below are based on voluntary post-approval reporting. The categories of adverse event reports are listed below in decreasing order of frequency by body system.

Gastrointestinal: Vomiting, diarrhea, inappetence, gastroenteritis, gastrointestinal bleeding, melena, gastrointestinal ulceration, hypoproteinemia, elevated pancreatic enzymes.
Hepatic: Abnormal liver function test(s), elevated hepatic enzymes, icterus, acute hepatitis.
Hematological: Anemia, hemolytic anemia, thrombocytopenia, prolonged bleeding time.
Neurological/Behavioral/Special Senses: Ataxia, paresis, aggression, sedation, hyperactivity, disorientation, hyperesthesia, seizures, vestibular signs, keratoconjunctivitis sicca.
Renal: Polydipsia, polyuria, urinary incontinence, azotemia, acute renal failure, proteinuria, hematuria.
Dermatological/Immunological: Pruritus, dermatitis, edema, alopecia, urticaria.
Cardiovascular/Respiratory: Tachycardia, dyspnea.

In rare situations, death has been reported as an outcome of some of the adverse responses listed above. To report suspected adverse reactions, or to obtain technical assistance, call (800) 477-1365.

SAFETY

In target animal safety studies, etodolac was well tolerated clinically when given at the label dosage for periods as long as one year (see Precautions).

Oral administration of etodolac at a daily dosage of 10 mg/kg (4.5 mg/lb) for twelve months or 15 mg/kg (6.8 mg/lb) for six months, resulted in some dogs showing a mild weight loss, fecal abnormalities (loose, mucoid, mucosanguineous feces or diarrhea), and hypoproteinemia. Erosions in the small intestine were observed in one of the eight dogs receiving 15 mg/kg following six months of daily dosing.

Elevated dose levels of EtoGesic (etodolac), i.e.≥40 mg/kg/day (18 mg/lb/day, 2.7X the maximum daily dose), caused gastrointestinal ulceration, emesis, fecal occult blood, and weight loss. At a dose of ≥80 mg/kg/day (36 mg/lb/day, 5.3X the maximum daily dose), 6 of 8 treated dogs died or became moribund as a result of gastrointestinal ulceration. One dog died within 3 weeks of treatment initiation while the other 5 died after 3-9 months of daily treatment. Deaths were preceded by clinical signs of emesis, fecal abnormalities, decreased food intake, weight loss, and pale mucous membranes. Renal tubular nephrosis was also found in 1 dog treated with 80 mg/kg for 12 months. Other common abnormalities observed at elevated doses included reductions in red blood cell count, hematocrit, hemoglobin, total protein and albumin concentrations; and increases in fibrinogen concentration and reticulocyte, leukocyte, and platelet counts.

In an additional study which evaluated the effects of etodolac administered to 6 dogs at the labeled dose for approximately 9.5 weeks, the incidence of stool abnormalities (diarrhea, loose stools) was unchanged for dogs in the weeks prior to initiation of etodolac treatment, and during the course of etodolac therapy. Five of the dogs receiving etodolac, versus 2 of the placebo-treated dogs, exhibited excessive bleeding during an experimental surgery. No significant evidence of drug-related toxicity was noted on necropsy.

STORAGE CONDITIONS

Store at controlled room temperature, 15-30°C (59-86°F).

HOW SUPPLIED

EtoGesic (etodolac) is available in 150, 300 and 500 mg single-scored tablets and supplied in bottles containing 7, 30 and 90 tablets.

NDC 0856-5520-03 – 150 mg – bottles of 7
NDC 0856-5520-04 – 150 mg – bottles of 30
NDC 0856-5520-05 – 150 mg – bottles of 90
NDC 0856-5530-03 – 300 mg – bottles of 7
NDC 0856-5530-04 – 300 mg – bottles of 30
NDC 0856-5530-05 – 300 mg – bottles of 90
NDC 0856-5550-03 – 500 mg – bottles of 7
NDC 0856-5550-04 – 500 mg – bottles of 30
NDC 0856-5550-05 – 500 mg – bottles of 90

REFERENCES

1. Vane, JR, RM Botting. Overview - mechanisms of action of anti-inflammatory drugs. In Improved Non-steroid Anti-inflammatory Drugs - COX-2 Enzyme Inhibitors. J Vane, J Botting, R Botting (ed.) 1996. Kluwer Academic Publishers. Dordrecht, The Netherlands.
2. Glaser, KB. Cyclooxygenase selectivity and NSAIDs: cyclooxygenase-2 selectivity of etodolac (Lodine®). *Inflammopharmacol* (1995) 3:335-345.
3. Gervais, F, RR Martel, E Skamene. The effect of the non-steroidal anti-inflammatory drug etodolac on macrophage migration *in vitro* and *in vivo*. *J. Immunopharmacol* (1984) 6:205-214.
4. Cayen, MN, M Kraml, ES Ferdinandi, EL Greselin, D Dvornik. The metabolic disposition of etodolac in rats, dogs, and man. *Drug Metab. Revs.* (1981) 12:339-362.

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

00353 Revised February 2003 5530F

FORT DODGE ANIMAL HEALTH
LABEL CONTROL

Revision:	1
Operator:	hal
Date:	03May01
Product I.D.#:	5551A
Product Name:	EtoGesic
Size:	$1^{3}/_{8}$" x $4^{1}/_{4}$"
Product Type:	Label / 500 mg (7 tabs)
File Location:	V1/PF/5551A/5551A
To Disk:	
Rev. Level:	

PMS 287
PMS 185

PMS 347

NDC 0856-5550-03

EtoGesic®

(etodolac)

FORT DODGE®

FOR ORAL USE IN DOGS ONLY

500 mg

7 TABLETS

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 141-108, Approved by FDA

CLIENT INFORMATION SHEET SHOULD BE READ PRIOR TO USE.

INDICATIONS: EtoGesic (etodolac) is recommended for the management of pain and inflammation associated with osteoarthritis in dogs.

DOSAGE AND ADMINISTRATION: The recommended dose of etodolac in dogs is 10 to 15 mg/kg body weight (4.5 to 6.8 mg/lb) administered once daily. Read package insert before use.

WARNINGS: Keep out of reach of children. Not for human use. For use in dogs only. Do not use in cats.

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

CLIENT INFORMATION SHEET SHOULD BE READ PRIOR TO USE. DO NOT OBSCURE THIS PORTION OF THE LABEL WHEN DISPENSING.

Lot

Exp. Date

5551A

10003

FORT DODGE ANIMAL HEALTH
LABEL CONTROL

Revision:	1
Operator:	hal
Date:	03May01
Product I.D.#:	5553A
Product Name:	EtoGesic
Size:	$1^{5}/_{8}$" x $3^{7}/_{8}$"
Product Type:	Label / 500 mg (30 tabs)
File Location:	V1/PF/5553A/5553A
To Disk:	
Rev. Level:	

PMS 287
PMS 185
PMS 347

NDC 0856-5550-04

EtoGesic®

(etodolac)

FORT DODGE®

FOR ORAL USE IN DOGS ONLY

500 mg

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Fort Dodge Animal Health
Fort Dodge, Iowa 50501 USA

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Lot

Exp. Date

5553A

20002